Comments on Dose-Response Assessment of Cancer from Inorganic Arsenic

Kenneth G. Brown

October 19, 2005

Problems associated with interpretation of the S.W. Taiwan data set for the objective of dose-response assessment were described in a previous submission to the Arsenic Panel. It was noted that cancer mortality was not predictable from the available data that was grouped at the village level. Those data, as used in the EPA draft dose-response assessment, consist of a villages dose (the median arsenic concentration of wells tested for arsenic) along with records of bladder and lung cancer mortality by age and gender. It was concluded that either additional covariate information was needed, the well test data were unreliable, or both.

Whatever the cause, it was clear that the village dose in the S.W. Taiwan data could have only a small explanatory capability for variation in age-adjusted cancer mortality. Some claims have been made, however, that dose-response estimation from the S.W. Taiwan data is creditable, in spite of the ecological exposure data and clear statistical evidence to the contrary, and that studies in Argentina and Chile provide supporting evidence. The latter claim is addressed in this note.

Risk assessment is often described as having four steps of which the first two are hazard identification and dose-response assessment (NAS, 1983). The former is defined as "the process of determining whether exposure to an agent can cause an increase in the incidence of a health condition (cancer, birth defect, etc.)", whereas the latter is defined as "the process of characterizing the relation between the dose of an agent administered or received and the incidence of an adverse health effect in exposed populations and estimating the incidence of the effect as a function of human exposure to the agent" (NAS, 1983, p. 19). The data requirements for dose-response are much higher because of the need to estimate the functional relationship between dose and response statistically, whereas hazard identification only requires sufficient evidence of increased response at a high dose, or evidence of an upward trend, that is reasonably attributable to the exposure agent.

In the absence of biological evidence of a mode-of-action, hazard identification and dose-response may rely heavily on statistical inference from epidemiological data, which has been the case with inorganic arsenic in drinking water (although the various mode(s)-of-action by inorganic arsenic may indicate a sublinear dose-response relationship for carcinogenicity). There are sufficient epidemiological studies linking arsenic in drinking water to cancer incidence or mortality to establish a cancer hazard. These typically consist of a significantly increased relative risk or standardized mortality ratio at high dose or even evidence of an upward trend in these measures as dose increases. That falls short of estimating the magnitude of response as a function of dose, however, as needed for prediction of response and extrapolation of response to low doses common in the U.S.

What should be interpreted as a test for trend is sometimes over-interpreted as a dose-response curve. For example, a least-squares straight-line fit of response to dose is often used to test for trend, since it is sensitive to an upward increase in response with dose even if the correct form of the dose-response curve is nonlinear. In general, fairly detailed and reliable data on the relationship of dose and response at several dose levels is required for dose-response assessment, along with statistical evidence of goodness-of-fit. That has been lacking for inorganic arsenic in drinking water.

Two studies in Argentina and Northern Chile serve the objective of hazard identification and confirm the evidence from the S.W. Taiwan data of increased risk of bladder and/or lung cancer from long-term exposure to relatively high levels of arsenic in drinking water (Hopenhayn-Rich et al., 1998; Smith et al., 1998). These studies are ecological[1], however, and thus do not serve the objective of dose-response assessment. That is made explicit in Smith et al. (1998), which states "Dose-response relations are not identifiable from this mortality study because individual exposure data are lacking." That is the same shortcoming that makes the S.W. Taiwan database unsuitable for dose-response assessment. As noted by Greenland and Robins (1994), a number of authors have pointed out that ecological relative-risk estimates can be subject to biases not present in estimates from individual-level observational studies of the same populations (case-control and cohort studies).

A third study that affirms a lung cancer hazard associated with arsenic in drinking water was conducted in northern Chile (Ferreccio et al., 2000). It indicates a clear upward trend in odds ratios for data grouped by broad exposure categories (0-10, 10-29, 30-59, 60-89, 90-199, 200-399, 400-699, 700-999 µg/L). The 0-10 µg/L exposure group is used as the referent group for calculating odds ratios. According to the authors, their study is the first to provide individual exposure data potentially useful for dose-response. They claim that their data (their Tables 5 and 6) are consistent with supralinearity, but no dose-response assessment is provided and the data in the two tables are grouped by exposure category similar to that shown above.

Data at the individual level in the study of Ferreccio et al. would need to be used for dose-response assessment before conclusions could be drawn about sublinearity or supralinearity, but the study is not suitable for that objective for several reasons. As noted by EPA, the data are "not precise enough for quantified risk assessments" due to wide and overlapping confidence intervals (US EPA 2005, p.11). The EPA is interested in arsenic levels as low as 10 µg/L, which it has set as a maximum contaminant level, but that value is in the referent group (it is actually included in both the referent group and the lowest exposure group, but that is an inconsequential error).

A more serious concern is that the study of Ferreccio et al. is admittedly biased because the control selection criteria were not fully adhered to, resulting in relatively more controls being chosen from the highly exposed city of Antofagasta, and fewer controls selected from the lower exposure city of Arica (their Table 2). The authors conclude in their results section that the likely direction of bias would be underestimation of the odds ratio at higher doses and overestimation at lower doses. Thus, while this bias may not affect hazard identification, it would affect dose-response assessment and lead to upward bias in estimates at low arsenic levels.

A further limitation for the objective of dose-response assessment in the study of Ferreccio et al. is the use of average individual exposures from arsenic in drinking water. As discussed in the article and apparent in their Table 1, the exposure could vary several fold for individuals in most locations in Region II. Without detailed data on how the mode(s)-of-action of arsenic may change with dose, it is not at all clear that cancer risk at an average of high and low exposure levels would be the same as constant exposure at the

average exposure, as would be implicitly assumed with averages. That is probably not consequential for hazard identification but would need to be considered in dose-response assessment.

In conclusion, the three studies cited all contribute to establishing chronic exposure to arsenic in drinking water at sufficiently high concentrations as a hazard for internal cancers. Two of the three studies are not suitable for dose-response assessment because they are ecological, lacking individual exposure data. The third study collected individual exposure data but has other serious shortcomings for the objective of dose-response assessment. None of these three studies provide useful information for assessing the dose-response relationship for inorganic arsenic at low doses. In fact, both the S.W. Taiwan data set and Ferreccio et al. likely overestimate the risk in the low dose region.

[1] Unlike an individual-level study, an ecological study does not link individual outcomes events to individual exposure or covariate histories, nor does it link individual exposure and covariate histories to one another (Greenland and Robins, 1994).

References

NAS. 1983. *Risk Assessment in the Federal Government: Managing the Process.* National Academy Press, D.C.

Ferreccio, C., C. Gonzalez, V. Milosavjlevic, V. et al. 2000. Lung cancer and arsenic concentrations in drinking water in Chile. *Epidemiology.* 11(6):673-679.

Greenland, S. and J. Robins. 1994. Invited commentary: Ecologic studies - biases, misconceptions, and counterexamples. *Am. J. Epidemiol.* 139:747-760.

Hopenhayn-Rich, C., M.L. Biggs, and A.H. Smith. 1998. Lung and kidney cancer mortality associated with arsenic in drinking water in Cordoba, Argentina. *Int. J. Epidemiol.* 27:561-569.

Smith, A.H., M. Goycolea, R. Haque, et al. 1998. Marked increase in bladder and lung cancer mortality in a region of northern Chile due to arsenic in drinking water. *Am. J. Epidemiol.* 147:660-669.

U.S. EPA. 2005. Issue Paper: Inorganic arsenic cancer slope factor. July 23, 2005. At www.epa.gov/waterscience/sab/AsIssues_SAB.pdf. U. S. Environmental Protection Agency.